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Linking Morphogen and Chromatin in the Hair Follicle

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In this issue of *Developmental Cell*, Xiong et al. (2013) identify a critical role for the chromatin remodeler Brg1 in hair follicle stem cell maintenance and epidermal repair. Brg1 interacts with the Shh signaling pathway to create a positive feedback loop that fuels hair follicle growth.

Chromatin remodeling factors are known to be critical for tissue development. Recent studies have implicated chromatin remodelers as also being important for epithelial tissue maintenance and repair. Additionally, efforts to create an epigenetic map for hair follicle cells have set a foundation for defining the link between epigenetic factors and hair follicle regeneration (Zhang et al., 2012). Brahma-related gene 1 (Brg1) is an ATP-dependent chromatin remodeling factor that is a member of the SWI/SNF family. Brg1 plays a role in many developmental processes and has also been implicated in cell proliferation and cancer (Hargreaves and Crabtree, 2011). In a study published in this issue of *Developmental Cell*, Xiong, et al. (2013) evaluate the role of Brg1 in hair follicle maintenance and skin repair.

Hair follicles constantly regenerate, cycling between rest, growth, and destruction phases. This continuous regeneration is fueled by two cell populations that reside at the bottom of the follicle—the hair follicle stem cells, called bulge (Cotsarelis et al., 1990) and the stem cell progeny—called hair germ (Greco et al., 2009; Rompolas et al., 2012). Xiong and colleagues (2013) found that Brg1 expression is induced at the transition from rest to growth in the hair follicle. Upon growth (anagen), Brg1 is expressed in the stem and progenitor cells (bulge and hair germ, respectively), as well as in the transient-amplifying (matrix) cells. To address the potential role of Brg1 in the hair follicle stem cell compartment, the authors created a Nfatc1Cre;Brg1$^{f/f}$ mouse, which removed Brg1 from the stem cells in the first resting (telogen) stage. Removal of Brg1 from the stem cell and hair follicle progeny leads to dramatic reduction in hair follicle maintenance, loss of stem cell markers, and, ultimately, hair loss. Hair follicle stem cells can also contribute to epidermal wound healing (Ito et al., 2005). Brg1 null hair follicles were unable to properly elicit a depilation or epidermal wound-induced repair response. Consistent with these findings, the authors found that the bulge stem cell pool reduced over time in the absence of Brg1. This corresponded with in vitro studies demonstrating that human bulge stem cells transfected with Brg1 small interfering RNA were less proliferative than controls. This effect was coupled with an increased expression of the cell-cycle inhibitor p27^{Kip1}. This work thus determines that Brg1 is necessary for stem cell proliferation and activation in physiological and wound-healing conditions.

To understand the molecular mechanism by which Brg1 regulates hair follicle bulge stem cells, Xiong et al. (2013) explored the possibility of crosstalk between the epigenetic factor Brg1 and known regulators of hair follicle growth. The authors discovered a molecular feedback loop between Brg1 and an evolutionarily conserved morphogen, Sonic Hedgehog (Shh). Shh signaling is known to tightly control hair follicle regeneration (Silva-Vargas et al., 2005). Xiong et al. (2013) show that Brg1 regulates Shh by first demonstrating that Shh expression is dramatically reduced in Brg1 null hair follicles. They then find through chromatin immunoprecipitation analysis of skin combined with a luciferase reporter system that Brg1 binds to and activates the Shh promoter. Finally, the authors found that Brg1 was able to physically bind to NFκB, a transcription factor known to enhance Shh expression (Schmidt-Ullrich et al., 2006). Thus, their data suggest that Brg1 and NFκB cooperatively activate the *Shh* promoter.

Interestingly, Xiong and colleagues further showed that Shh signaling has upstream effects on Brg1 expression. A Shh agonist, SAG, known to accelerate hair growth (Paladini et al., 2005), was unable to initiate growth in Brg1-deficient hair follicles. The authors found that SAG enhanced expression of Brg1 in hair follicle stem cells and progeny. They also showed that downstream effectors of Shh signaling, Gli1 and Gli2, were both able to bind and activate the Brg1 promoter.

Together, these data show that Brg1 is a chromatin remodeler with critical roles in hair follicle maintenance and epidermal repair. In addition, this study (Xiong et al., 2013) provides clear evidence that Brg1 can directly regulate Shh signaling at a transcriptional level. Furthermore, the authors propose that Shh and Brg1 have reciprocal effects on each other and may represent a positive feedback loop.

These findings have broad implications for the role of chromatin remodelers on stem cell biology and tissue regeneration, shedding light on how epigenetic factors such as Brg1 can activate resting stem cell populations. Understanding this molecular switch will enable researchers to effectively direct cells and tissues to a targeted function state. Integration of the Brg1-Shh feedback loop with other well-established hair follicle growth regulators will provide a more complete framework for deciphering the complexity of tissue regeneration. How

this molecular circuit is sensed and perceived by different tissues and cell types remains unclear but will be vital to our understanding of tissue dynamics.

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New Ways to Gather Grains

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A crucial step in cereal grass domestication is acquisition of seed retention in the inflorescence/seed head for efficient harvesting. Reporting in *Nature Genetics*, Ishii and colleagues (2013) show that a change in inflorescence architecture is sufficient to increase seed retention, providing an alternative pathway toward cereal grass domestication.

Domestication is of great interest to agricultural researchers and evolutionary biologists alike. In the cereal grasses, it has long been recognized that a crucial step in domestication is to retain seed in the inflorescence (seed head) to enable efficient harvesting. The evolution of nonshattering seed heads is thus one of the key markers for domestication in cereal grasses. It is a defining difference between domesticated crops and their wild ancestors now, and it is a sure sign of domestication when it occurs in the archaeological record. A nonshattering seed head is thought of as a preeminent domestication trait not only because the retention of seeds makes for easier human harvesting but also because retention is maladaptive for wild grasses that need to disperse their seeds easily and widely. Much work has been done on the genetic architecture of shattering, which ranges from a single major effect locus in sorghum to three or four loci in rice (Zhang et al. 2009; Lin et al. 2012; Zhou et al. 2012). An obvious mechanism to stop shattering is to modify or eliminate the abscission layer between seed and stalk that allows seed dispersal, and several genes have been identified that control this change. However, Ishii and colleagues (2013) now report in *Nature Genetics* that even without modification of the abscission zone, changing the inflorescence (seed head) architecture can significantly increase seed retention and reduce outbreeding.

A full understanding of domestication has not yet been achieved, although recent archaeological findings and modeling approaches suggest that it is a protracted process, with the nonshattering phenotype taking two to three thousand years to become widespread in wheat and in rice (Purugganan and Fuller, 2010). Interestingly, a prediction made by Andy Paterson in 1995—that the same genes would underlie the shattering phenotype in all grasses—has been at least somewhat validated by recent investigations of the *SH1* gene in sorghum (Paterson et al. 1995; Lin et al. 2012). This gene has been shown to be orthologous with one under selection in rice and colocalizes with quantitative trait loci for shattering in foxtail millet and maize. However, the major genes controlling shattering in rice—*sh4* and *qSH1*—do not appear to be involved in the control of shattering in other cereal domestications (Konishi et al. 2006; Li et al. 2006). Intriguingly, neither of the mutations in the major-effect shattering loci that nowadays differentiate wild rice from domesticated are sufficient by themselves to produce the nonshattering phenotype in wild rice (Ishikawa et al. 2010). This implies that single gene changes in the wild ancestor may not have had immediate phenotypic effects until the overall genetic framework was sufficiently modified by other mutations. Under this scenario, other mechanisms to enhance seed retention would also have been selected upon, as shown by Ishii and colleagues (2013), who propose an alternative mechanism to enhance seed retention involving changes to the architecture of the inflorescence.

In *Oryza rufipogon*, the wild progenitor of domesticated rice (*O. sativa*), the seed